REMARKS/ARGUMENTS

The foregoing amendments in the specification and claims are of a formal nature, and do not add new matter.

Prior to the present amendment, Claims 28-47 were pending in this application and were rejected on various grounds. With this amendment, Claims 37 and 41-43 have been canceled without prejudice and Claims 28-36 and 38-39 have been amended to clarify what Applicants have always regarded as their invention. The amendments to the specification and claims are fully supported by the specification and claims as originally filed and do not constitute new matter. Amendments to Claims 28-36 can be found in Example 152 at least on page 509, line 30 of the specification.

Claims 28-35, 38-40 and 44-47 are pending after entry of the instant amendment. Applicants expressly reserve the right to pursue any canceled matter in subsequent continuation, divisional or continuation-in-part applications.

In addition, Applicants request the PTO to take note of the Revocation and Power of Attorney and Change of Address filed on February 28, 2003, and kindly direct all future correspondence to the address indicated, *i.e.*, to:

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1. Formal Matters

Applicants thank the Examiner for entering the Preliminary Amendment filed on December 12, 2001 and August 29, 2002. Applicants also thank the Examiner for entering the Information Disclosure Statement filed on November 5, 2002 into the record.

2. **Priority**

The Examiner alleges that "[d]ue to the excessive number of applications from which the present application claims benefit, priority cannot be determined."

The Examiner's attention is respectfully directed to the Preliminary Amendment filed on August 29, 2002, which states that the present application is "a continuation of, and claims priority under 35 U.S.C. §120 to, U.S. Patent Application Serial No. 09/946,374 filed 9/4/2001, which is a continuation of, and claims priority under 35 U.S.C. §120 to, PCT Application PCT/US00/04342 filed 2/18/2000, which is a continuation-in-part of, and claims priority under 35 U.S.C. §120 to, U.S. Patent Application Serial No. 09/403,297 filed 10/18/1999, now abandoned, which is the National Stage filed under 35 U.S.C. §371 of PCT Application PCT/US99/20111 filed 9/1/1999, which claims priority under 35 U.S.C. §119 to U.S. Provisional Application Serial No. 60/101,916 filed 9/24/1998."

As discussed below, Applicants rely on Assay 54 (Rat Utricular Supporting Cell Proliferation Assay) (Example 152) for patentable utility which was first disclosed in PCT/US00/04342, filed on February 18, 2000, priority to which has been claimed in this application. Accordingly, the present application is entitled to at least the February 18, 2000 priority date. In support, Applicants enclose herewith page 525, describing Assay 54 (Example 98), of the PCT Publication WO 00/78961, corresponding to PCT Application PCT/US00/04342.

3. **Information Disclosure Statement**

In response to the Examiner's assertion that references 1 and 2 in the Information Disclosure Statement filed on November 5, 2002 are not in proper format, Applicants file herewith, an Information Disclosure Statement listing each reference of the "Blast Search" separately and including authors/inventors, relevant accession numbers and publication dates. Applicants respectfully request that the listed information be considered by the Examiner and be made of record in the above-identified application.

4. **Specification**

As requested by the Examiner, the specification has been amended to remove embedded hyperlink and/or other form of browser-executable code, and the title of the application has been amended to recite a new, descriptive title indicative of the invention to which the claims are directed.

Further, Applicants have amended the specification to clearly recite the conditions of the deposits made under the Budapest Treaty.

5. **Claim Objections**

Claims 28-47 were objected to for reciting a Figure number and a SEQ ID NO. Applicants submit that the cancellation of Claims 37 and 41-43 renders the objection to these claims moot. Further, Applicants submit that Claims 28-35 have been amended to only recite SEQ ID NO. Accordingly, Applicants respectfully request that the Examiner withdraw its objection to Claims 28-36, 38-40 and 44-47.

6. **Claim Rejections Under 35 U.S.C. §101**

Claims 28-47 were rejected under 35 U.S.C. §101 allegedly "because the claimed invention is not supported by either a specific, substantial and credible asserted utility or a well established utility." For the reasons outlined below, Applicants respectfully disagree.

Applicants submit that the cancellation of Claims 37 and 41-43 renders the rejection of these claims moot.

Utility – Legal Standard

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. §101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic without also identifying the conditions that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "[t]he basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. §2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, **any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient**, at least with regard to defining a "'substantial'" utility.'" (M.P.E.P. §2107.01, emphasis added.) Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P. §2107 II (B) (1) gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Finally, the Utility Guidelines restate the Patent Office's long established position that any asserted utility has to be "credible." "Credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record . . . that is probative of the applicant's assertions." (M.P.E.P. §2107 II (B) (1) (ii)) Such a standard is presumptively satisfied unless the logic underlying the assertion is seriously flawed, or if the facts upon which the assertion is based are inconsistent with the logic underlying the assertion (Revised Interim Utility Guidelines Training Materials, 1999).

Proper Application of the Legal Standard

As discussed above, Applicants further rely on Assay 54 (Example 152) for priority and to establish patentable utility for the PRO1340 polypeptides and the encoding nucleic acids thereof. Accordingly, the present application is entitled to the effective filing date of

February 18, 2000.

Assay 54 was used to identity polypeptides that can act as potent mitogens for inner ear supporting cells. These supporting cells are auditory hair cell progenitors and, therefore, the identified polypeptides are useful for inducing the regeneration of auditory hair cells and treating hearing loss in mammals. In particular, this assay was performed as follows. Rat UEC-4 utricular epithelial cells were aliquoted into 96 well plates with a density of 3000 cells/well in 200 μl of serum- containing medium at 33°C. The cells were cultured overnight and were then switched to serum-free medium at 37°C. Various dilutions of PRO1340 polypeptides (or nothing for a control) were then added to the cultures and the cells were incubated for 24 hours. After the 24 hour incubation, ^{3}H-thymidine (1 μCi/well) was added and the cells were then cultured for an additional 24 hours. The cultures were then washed to remove unincorporated radiolabel, the cells harvested and Cpm per well determined. Cpm of at least 30 % or greater in the PRO1340 polypeptide treated cultures as compared to the control cultures was considered a positive in the assay. As disclosed in PCT/US00/04342, which has been incorporated by reference in its entirely in the present application, PRO1340 was tested positive in Assay 54, indicating that this polypeptide is a potent mitogen and can be used for treating hearing loss.

Proliferation of supporting cells in the inner ear is the early major event occurring during hair cell regeneration after acousetic trauma or aminoglycoside treatment. Because the supporting cells of in the inner ear epithelium are most likely the progenitor cells for the hair cells, the proliferation of the supporting cells is critical for the replacement of the lost hair cell and supporting cells that are capable of converting into new hair cells.

Applicants submit that Assay 54, rat utricular supporting cell proliferation assay, was developed by Zheng *et al* as early as in 1997, which is prior to the effective filing date of the present application, and was considered in the art as a rapid and reliable approach for the measurement of proliferation of progenitor cells and for identifying new mitogenic agents for treating hearing loss. (Zheng *et al.*, *J Neurosci.* 17(1):216-26 (1997) - copy enclosed).

Zheng *et al.* considered this assay as "a rapid, reliable tritiated thymidine assay for measurement of the progenitor cell DNA synthesis in purified, partially dissociated postnatal rat

inner ear epithelial cell cultures." (See page 217, column 1). Using this rapid, convenient assay, Zheng *et al.* examined the effects of a panel of 30 growth factors on the proliferation of utricular supporting cells. These included known and commonly studied mitogens and differentiating and survival factors in the nervous system. Zheng *et al.* discovered that several FGF family members, IGF-1, IGF-2, TGF-α, and EGF, are mitogens for the utricular supporting cells. Among them, FGF-2 is the most potent mitogen. These results were confirmed by BrdU immunocytochemistry. Inclusion of neutralizing antibodies against FGF-2 or IGF-1 in the medium reduced utricular epithelial cell proliferation. Thus, these results suggest that FGF-2 and IGF-1 are candidate molecules regulating proliferation of the inner ear supporting cells. In particular, FGF-2 is a physiological growth factor during regeneration of new hair cells following challenge by aminoglycosides or noise.

In order to confirm that this culture system represents a population of utricular supporting cells, Zheng *et al.* examined the expression of the cell surface markers typical for the supporting cells via immunocytochemical staining. Immunocytochemical staining with different types of cell markers revealed that these cultured cells expressed epithelial cell antigens, including a tight junction protein (ZO1), F-actin, and cytokeratin. They did not express antigens for other types of cells, such as glial filament protein (GFAP), the oligodendrocyte antigen (myelin), neurofilament protein, or fibroblast antigens, vimentin and Thy1.1. (See Table 1 and page 219, column 1). Accordingly, these results suggest that the cultured cells are pure epithelial cells, and the vast majority of the surviving cells in the cultures represented a population of utricular supporting cells.

Zheng *et al.* finally concluded that, "we have established a purified mammalian utricular epithelial cell culture, which allows us to rapidly examine possible effects of known and novel growth factors on supporting cell proliferation, an early phase during normal development and regeneration of new hair cells." (See page 226, column 2).

Based on the above arguments, Applicants have clearly demonstrated a credible, specific and substantial asserted utility for the PRO1340 polypeptide and its encoding nucleic acid, for

example, as a mitogenic factor for treating hearing loss. Further, based on this utility and the disclosure in the specification, one skilled in the art at the time the application was filed would know how to use the claimed polypeptides.

In view of the above, Applicants respectfully request the Examiner to reconsider and withdraw the rejection of Claims 28-36, 37-40 and 44-47 under 35 U.S.C. §101.

7. **Claim Rejections Under 35 U.S.C. §112, Second Paragraph (Enablement)**

A. Claims 28-47 stand rejected under 35 U.S.C. §112, first paragraph, allegedly for "failing to adequately teach how to use the instant invention." Specifically, the Examiner asserts that "since the claimed invention is not supported by a specific, substantial and credible asserted utility or a well established utility . . . one skilled in the art clearly would not know how to use the claimed invention."

In response to the rejection under 35 U.S.C. §101, Applicants have shown above that the specification discloses at least one substantial, specific and credible utility for the PRO1340 polypeptide and its encoding nucleic acid. Further, without acquiescing to the Examiner's position in the current rejections, and without prejudice to further prosecution of the subject-matter in one or more continuation or divisional applications, Claims 28-32 (and, as a consequence, those claims dependent from the same) have been amended to recite "the encoded polypeptide promotes proliferation of inner ear supporting cells." Since the claimed genus is now characterized by a combination of structural and functional features, any person of skill would know how to make and use the invention without undue experimentation based on the general knowledge in the art at the time the invention was made. As the M.P.E.P. states, "The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation" *In re Certain Limited-charge cell Culture Microcarriers, 221 USPQ 1165, 1174* (Int'l Trade Comm'n 1983), *aff'. sub nom., Massachusetts Institute of Technology v A.B. Fortia,* 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985) M.P.E.P. §2164.01.

In view of the discussions above regarding the utility of the polypeptides, Applicants submit that Claims 28-36, 38-40 and 44-47 satisfy the enablement requirement because one

skilled in the art would know how to make and use the claimed polypeptides. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

B. Claims 28-47 stand rejected under 35 U.S.C. §112, first paragraph, allegedly for "containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention." The Examiner specifically notes that "the deposit of the biological material is considered necessary for the enablement of the current invention."

Applicants submit that the cancellation of Claims 37 and 41-43 renders the rejection of these claims moot.

Applicants disagree with the Examiner's assertion that the deposit was necessary for enablement of the current invention. The current invention is fully enabled by the disclosure of the present application, including the sequence of PRO1340 and its coding sequence. Further, as discussed above, the foregoing amendment to the specification corrects the address of ATCC, and further elaborates on the conditions of the deposit, which was made for patent purposes, under the terms of the Budapest treaty.

Nevertheless, Applicants enclose herewith a copy of the deposit receipt indicating that DNA66663-1598 deposit, ATCC Deposit No. 203268, was made by Applicants on September 22, 1998.

In addition, as stated above, Applicants respectfully submit that the specification clearly discloses that the deposit was made under the Budapest Treaty and provides the accession number for the deposit, the date of the deposit, the description of the deposited material, and the name and address of the depository starting on page 517, line 1 of the specification.

Applicants further submit that the specification has been amended to recite that the deposit will be maintained "for 30 years from the date of deposit and for at least five (5) years after the most recent request for the furnishing of a sample of the deposit received by the depository" and to recite that "all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of the pertinent

U.S. patent."

Accordingly, Applicants believe that the present rejection should be withdrawn.

C. The Examiner further alleges that even if Claims 28-47 possessed utility under 35 U.S.C. §101, which Applicants assert they do, Claims 28-47 would still be rejected under 35 U.S.C. §112, first paragraph, "because the specification, while then being enabling for SEQ ID NO:228 and 229, does not reasonably provide enablement for polynucleotides or polypeptides having at least 80%, 85%, 90%, 95% or 99% sequence identity to SEQ ID NO:228 or 229, to the protein encoded by ATCC No. 203268, for the extracellular domain thereof, or for vectors and host cells containing these polynucleotides." In addition, the Examiner alleges that "[t]he claims are too broad ... because the claims have no functional limitation."

For all the reasons discussed above, Applicants respectfully disagree with the Examiner. As described above, Applicants respectfully submit that the specification provides sufficient disclosure to establish a specific, substantial and credible utility for the PRO1340 polypeptide and its encoding nucleic acid. In addition, as amended, Claims 28-32 (and, as a consequence, those claims dependent from the same) now recite a functional limitation, namely that the encoded polypeptide promotes proliferation of inner ear supporting cells.

Accordingly, Applicants respectfully submit that it would not require undue experimentation for one of skill in the art to apply the teachings of the present disclosure so as to practice the invention of Claims 28-32 (and, as a consequence, those claims dependent from the same). The Examiner is therefore, respectfully requested to reconsider and withdraw the rejection of these claims under 35 U.S.C. §112, first paragraph.

8. <u>Claim Rejections Under 35 U.S.C. §112, First Paragraph (Written Description)</u>

Claims 28-47 are rejected under 35 U.S.C. §112, first paragraph, for allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention at the time the application was filed. In particular, the Examiner notes that "[t]he claims are drawn to

polynucleotides having at least 80%, 85%, 90%, 95% or 99% sequence identity with SEQ ID NO:228 as well as vectors and host cells[, without requiring] that the polynucleotides or encoded polypeptides of the present invention possess any particular biological activity . . . ."

Applicants submit that the cancellation of Claims 37 and 41-43 renders the rejection of these claims moot.

Without acquiescing to the propriety of this rejection, solely in the interest of expediting prosecution in this case, Applicants respectfully submit that amended Claims 28-32 (and, as a consequence, those claims dependent from the same) now recite a functional limitation that the encoded polypeptide promotes proliferation of inner ear supporting cells. Accordingly, it is no longer true that the claims are drawn to a genus of polynucleotides defined by sequence identity alone. Coupled with the general knowledge available in the art at the time of the invention, the specification provides ample written support for such polypeptides in Example 152 (page 509 of the specification) where assay for the ability of polypeptides to promotes proliferation of inner ear supporting cells is described. Thus, based on the high percentage of sequence identity and the described method to assay for polypeptides that promote proliferation of inner ear supporting cells, one skilled in the art would have known at the time of the invention, that the Applicants had possession of the claimed polynucleotides.

The Examiner is therefore respectfully requested to reconsider and withdraw the rejection of these claims for allegedly lacking written support.

9. Claim Rejections Under 35 U.S.C. §112, Second Paragraph

A. Claims 28-47 are rejected under 35 U.S.C. §112, second paragraph, for allegedly "being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." The Examiner notes that Claims 28-47 are vague and indefinite since "it is not clear whether or not the protein encoded by the polynucleotide of the present invention is a soluble protein (*e.g.*, protease), nor is it disclosed as being expressed on a cell surface." Accordingly, the Examiner asserts that the recitation of "extracellular domain" and the recitation of "the extracellular domain ... lacking its associated signal sequence" are

indefinite.

Applicants submit that the cancellation of Claims 37 and 41-43 renders the rejection of these claims moot. Further, without acquiescing to the propriety of this rejection, solely in the interest of expediting prosecution in this case, the term "extracellular domain ... lacking its associated signal sequence" is no longer present in Claims 28-33 (and, as a consequence, those claims dependent from the same).

Applicants submit that the term "extracellular domain" is a widely known and a commonly used scientific term which is clearly understood by those skilled in the art. Furthermore, the term "extracellular domain" or "ECD" is supported in the specification at least on page 299, lines 21-26, which discloses that " extracellular domain" or "ECD" refers to "a form of the PRO polypeptide which is essentially *free* of the transmembrane and cytoplasmic domains.... It will be understood that any transmembrane domains identified for the PRO polypeptides of the present invention are identified pursuant to criteria routinely employed in the art for identifying that type of hydrophobic domain." Additionally, Figure 132 clearly indicates one transmembrane domain, residues 762-784 of SEQ ID NO:229. Hence, one of skill in the art would know, based on the teachings of the instant specification and the knowledge in the art, the types of sequences described in the claims and what the scope of the invention is.

Accordingly, Applicants respectfully request that the rejection of Claims 28-36, 38-40 and 44-47 under 35 U.S.C. §112, second paragraph, be withdrawn.

10. Claim Rejections Under 35 U.S.C. §102

As discussed above, Applicants rely on Assay 54 (Rat Utricular Supporting Cell Proliferation Assay) (Example 152) for patentable utility which was first disclosed in PCT/US00/04342, filed on February 18, 2000, priority to which has been claimed in this application. Accordingly, the present application is entitled to at least the February 18, 2000 priority date.

Claims 28-47 are rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Baker *et al.*, WO200012708, publication date of November 30, 2000. Applicants submit that the

cancellation of Claims 37 and 41-43 renders the rejection of these claims moot. Claims 28-32 (and, as a consequence, those claims dependent from the same) have been amended to recite a functional limitation that the encoded polypeptide "promotes proliferation of inner ear supporting cells." Therefore, as amended, Claims 28-32 (and, as a consequence, those claims dependent from the same) are entitled to an effective filing date of February 18, 2000. Hence, Baker *et al.* is not prior art under 102(b) since its publication date is after the effective priority dates of this application. Accordingly, Applicants respectfully request that this rejection be withdrawn.

CONCLUSION

In conclusion, the present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited. Should there be any further issues outstanding, the Examiner is invited to contact the undersigned attorney at the telephone number shown below.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (Attorney's Docket No. **39780-2830 P1C56**).

Respectfully submitted,

Date: November 22, 2004

By: _____
Anna L. Barry (Reg. No. 51,436)

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